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Food and Drug Administration
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Memorandum

Division of Clinical Trial Design and Analysis
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Subject: BLA STN 103780 / 0
Comparative Study of Rebif to Avonex and Orphan Exclusivity

Through: K. Weiss, Director, DCTDA

To: BLA STN 103780 / 0 File

Summary

This memorandum provides, describes, and summarizes FDA's analyses of the direct comparative clinical trial that Serono conducted comparing Serono's Rebif to Biogen's Avonex. Both of these products are interferon betas for the treatment of multiple sclerosis (MS), a disabling and degenerative autoimmune disease characterized by inflammation and scarring of the myelin, or tissue that covers nerve fibers, in the brain and spinal cord. Avonex is FDA-licensed and has orphan drug exclusivity.

Serono conducted the comparative study in order to demonstrate that Rebif is clinically superior to Avonex so that FDA can license Rebif. Serono sought to show that Rebif provides a significant therapeutic advantage over and above that provided by Avonex, due to Rebif having greater effectiveness. The primary measurement of effectiveness that Serono used was the frequency of MS exacerbations or flare-ups. The secondary measurement of effectiveness was the number of MRI brain lesions.

CBER has reviewed the results of the study and has consulted extensively with FDA's Office of Orphan Product Development (OOPD) concerning the study, the interpretation of the results, and applicable standards under the orphan drug regulations. As described below, the comparative clinical study demonstrates that Rebif is more effective that Avonex such that it provides a significant therapeutic advantage over Avonex: 74.9% of study subjects taking Rebif were exacerbation-free versus 63.3% of Avonex subjects. This is a meaningful difference, because it means, among other things, that a patient on Rebif is 32% less likely to experience an MS exacerbation, which can substantially lower his or her quality of life for weeks or months. MS exacerbations can be manifested by paralysis, loss of vision, loss of control of bladder and bowel function, as well as other impairments. Furthermore, subjects on Rebif had fewer MRI brain lesions than subjects on Avonex.

FDA has considered a number of other issues concerning the adequacy of the comparative study and the safety and effectiveness of Rebif. As described below in the body of this memorandum, FDA has fully evaluated these issues and has determined that Rebif is clinically superior to Avonex.

Among other things, the design (including the baseline characteristics of the study population and endpoints) and the duration of the comparative study are adequate. The 6 month duration was sufficient to generate results that demonstrate that Rebif is clinically superior. As explained below, prior experience with interferon betas indicates that an effect of exacerbation reduction observed early in a clinical trial persists beyond 6 months. Furthermore, Serono has submitted the results from the comparative study through one year. These results confirm the data and effects observed at 6 months in the trial.

As detailed below, CBER has examined neutralizing antibody formation and its impact on effectiveness as seen in the comparative trial. The data do not establish that antibodies impair effectiveness. Moreover, patients on Rebif who developed antibodies were more likely to remain exacerbation-free than patients on Avonex.

The dose and frequency of Rebif administration that Serono studied in the comparative trial does not call into question the results of the trial. The argument that Serono simply gave subjects a higher dose of Rebif which generated short term effects, compared to Avonex, is not valid. Although Avonex and Rebif have been previously regarded as the same drug for orphan drug purposes, they are not biochemically comparable for purposes of non-orphan drug comparison.

Finally, FDA has fully considered the safety profile of Rebif. As described below, although Rebif may cause certain adverse events (AEs) more frequently than Avonex, FDA has determined that the severity and frequency of such AEs do not render Rebif unlicensable under Section 351 of the Public Health Service Act. Furthermore, under the orphan drug regulations, if Serono demonstrates that Rebif is clinically superior to Avonex on the basis of efficacy, Serono does not have to show that Rebif is safer than, or as safe as, Avonex.

Background: Interferon Beta use in Multiple Sclerosis

The first interferon beta for treatment of relapsing remitting multiple sclerosis (RRMS) became commercially available in July 1993 when Betaseron (interferon beta-1b) received marketing approval for this use. Betaseron was shown to be effective in reducing the incidence of exacerbations. Subsequently, a second interferon beta, Avonex (an interferon beta-1a) was shown to be effective for reducing the incidence of exacerbations and reducing the accumulation of physical disability. Betaseron received orphan drug designation prior to approval, and was still within the 7 year period of marketing exclusivity at the time Avonex was under review. However, Biogen, the manufacturer of Avonex, provided evidence that Avonex was not the same drug within the meaning of the orphan drug regulations, by showing Avonex was clinically superior over Betaseron. Specifically, Biogen supplied evidence showing a significant difference between the safety profiles of the two products with regard to skin necrosis at injection sites. Because Avonex and Betaseron were then deemed to be different drugs, Biogen received marketing approval for Avonex in May 1996. Biogen also has orphan drug designation for Avonex for this use and has a 7 year period of marketing exclusivity which expires in May 2003.

Serono, a third manufacturer of an interferon beta product, Rebif (an interferon beta-1a) also conducted clinical studies in relapsing-remitting MS. Serono completed their studies and submitted a Biologics License Application (BLA) for Rebif for use in MS in February 1998. The major safety and efficacy data came from the study XXXXXXXXXX, a three-group, controlled, randomized, double-blind study of doses of 22 µg or 44 µg vs. placebo. Based on review of the information supplied in the license application, FDA concluded that Rebif was safe and effective for use in the treatment of RRMS (see clinical review of J. Kaiser). However, under the framework of the orphan drug regulations, Rebif was regarded as a "same drug" as both Betaseron and Avonex. Serono was not able to supply evidence at that time that was sufficient to establish that Rebif was not the "same drug." As a consequence, Rebif could not be granted marketing approval until the bar of marketing exclusivity was removed, either by expiration of the exclusivity time period, or by Serono providing evidence that Rebif was not the "same drug."

Serono recognized that the Betaseron period of exclusivity would expire in July 2000, leaving only the Avonex marketing exclusivity as an issue after that date. Thus, in late 1999 Serono commenced a clinical study (Study XXXXXXXXXX), intended to be adequate and well-controlled, to show superior clinical efficacy of Rebif compared to Avonex. Serono's objective was to have this study provide sufficient evidence to enable marketing of Rebif prior to the expiration of Avonex's exclusivity period.

Orphan Drug Regulations

In implementing the Orphan Drug Act of 1983, the orphan drug regulations (21 CFR Part 316) allow a sponsor of an orphan-designated drug a 7 year period of marketing exclusivity for the "same drug" for the same approved indication. The regulations describe how to assess two products on a physical-chemical basis to determine if they should be regarded as the "same drug" for purposes of these regulations. The regulations further provide that even if the physical-chemical criteria for "same drug" are met, a demonstration of clinical superiority of the subsequent product compared to the originator product will enable a determination that the two products are in fact not the "same drug." Thus, the subsequent product may be given immediate marketing approval.

The regulations also describe the circumstances for determining clinical superiority. A new product can be considered clinically superior if greater effectiveness has been shown. Alternatively, a new product can also be considered clinically superior on the basis of greater safety in a substantial portion of the target populations. Lastly, "in unusual cases," a demonstration of some other form of a major contribution to patient care can be sufficient to regard the subsequent product as clinically superior.

An important aspect of this determination is that, per the regulations, demonstration of greater effectiveness will in most cases entail direct comparative clinical trials, whereas direct comparative trials for a demonstration of superior safety are expected to be necessary in only some cases. The regulations permit a determination of clinical superiority if the subsequent drug is shown to provide a significant therapeutic advantage over the approved drug in either safety or effectiveness. Additionally, the regulations do not state that clinical superiority must be based on overall risk-benefit being deemed superior for the subsequent product compared to the prior product. In fact,

the regulations indicate that only a selected aspect may constitute a sufficient basis to reach a conclusion of clinical superiority. That is, the aspects not selected by the sponsor for focus (e.g., safety when efficacy is selected; efficacy when safety is selected) do not require a comparative assessment. The regulations require neither that all aspects of known efficacy nor all aspects of safety be shown to be superior. Nor do the regulations indicate that other aspects of safety or efficacy be shown "comparable" when only one specific aspect of safety or efficacy is shown to be superior. Many other aspects of clinical performance of the drug may not be possible to compare. For example, while the regulations clearly indicate that direct, randomized clinical trials will usually be needed for a valid efficacy comparison, they indicate that a clinical superiority determination for superior safety may well be feasible without such direct comparisons. Consequently, knowledge of the comparison of efficacy could be entirely lacking (and somewhat inferior efficacy a real potential), yet a clinical superiority determination, based on safety, can be reached.

This last point is well-illustrated by the prior orphan drug history of the interferon beta products. When Biogen provided evidence to permit a determination that Avonex was not the same drug as Betaseron and gain marketing approval for Avonex, it was on the basis of a single specific AE . Apart from orphan drug considerations, FDA would have deemed Avonex safe and effective for approval. Because there were no direct comparative studies, many other aspects of comparative safety remain unevaluated, and a comparison with regard to efficacy has not been performed. Avonex may be as efficacious as Betaseron, or more or less efficacious . Thus, although a specific safety difference is known, most comparative aspects of safety, and all comparative aspects of efficacy, are unknown between Avonex and Betaseron .

Objective and Design of Serono Study XXXXXXXXXX

The objective of this study was to demonstrate whether Rebif was superior to Avonex in decreasing the incidence of exacerbations. See the BLA review of C. Rask for complete details and assessment. Briefly, this was a multicenter randomized two group study of Rebif at 44 µg subcutaneously (SC) 3 times per week (tiw) compared to Avonex at 30 µg intramuscularly (IM) weekly (qw). The primary efficacy outcome was the incidence of exacerbations through week 24, but all subjects were to continue in the controlled study through 48 weeks. Avonex was directed to be given according the recommended regimen in the FDA-approved labeling for Avonex, and Rebif according to the recommended regimen in Serono's proposed labeling. Commercially purchased Avonex was used in the study.

Serono noted that the difference in the administration route IM vs SC would require a double dummy design with 4 injections per week in an attempt to fully mask drug administration. This could make the study unpleasant for subjects, potentially decreasing subject compliance and retention for the full study, and yet might not actually achieve patient blinding as to group assignment due to the local skin reactions and systemic symptoms that would be physically and temporally associated with only one of the injection route regimens in each patient. Therefore, Serono elected to conduct the study open label, but with a blinded clinical evaluator. Each site operated with a treating physician who was, like the subjects, unblinded to treatment group. In addition, each site had an evaluating physician who remained blinded to assignment and had the responsibility for deciding whether changes in signs or symptoms qualified as an exacerbation.

Patients were to have complete neurological examinations by the evaluating physician every 12 weeks. However, in order to ensure that ascertainment of exacerbations was complete, subjects were instructed to telephone the clinical site in the event of any change in clinical status that might indicate a new exacerbation. When a subject called, and the site perceived that the reported changes had the potential to indicate a new exacerbation, the subject was told to come to the clinic to be evaluated. Additionally, so as to not rely solely upon the subject's perception in this unblinded study, during the first 6 months of the study the subjects were seen by the treating physician every month, and received phone calls from the site coordinator in the middle of each 4 week period between clinic visits. Thus, the study design provided for contact between the subject and the site every two weeks. During these phone calls or visits an assessment was made as to whether the subject had a change in symptoms suggesting the possibility of a new exacerbation. If so, the subject was instructed to come in to the site and the evaluating physician assessed the subject to confirm or reject the change in status as being an exacerbation. The change in frequency of clinical contacts after month 6 was related to the study objective, which was primarily to show the clinical superiority during a 6 month comparison period, with continuation of the observed effect through 12 months only as a secondary objective.

MRI scans were performed in addition to the clinical examinations. Patients had monthly T2 and Gadolinium-enhancing (Gd)-T1 scans during the first 6 months, and an additional T2 scan at month 12. Again, the change in frequency of scanning was related to the 6 month period as the primary focus of the study. MRI scan reading was performed blinded to group assignment. In order to permit an evaluation of Combined Unique (CU) lesions (see next paragraph) at baseline, a MRI scan set was obtained at screening and at baseline.

The primary endpoint of the study was the comparison of the proportion of patients who were exacerbation free during the first 6 months of the study. The major secondary endpoint was the chief MRI outcome of the number of CU active lesions per scan by subject. A CU active lesion was a lesion on either the T1 or T2 scan which was new or enlarging compared to the prior scan. A persistent Gd-enhancing lesion also qualified as an active lesion, and lesions in the same location on the T1 and T2 scans were counted as only a single active lesion. For each subject, the primary analysis consisted of averaging the number of CU active lesions on each of the monthly scans to provide an average number of CU active lesions per month for that patient.

Conduct of Study XXXXXXXXXX

Study XXXXXXXXXX enrolled 677 subjects at 56 study centers, 338 patients were randomized to receive Avonex and 339 patients were randomized to receive Rebif. The 37 study sites in the US enrolled 65% of the subjects. There were 15 sites in Europe enrolling 24% of subjects and 4 sites in Canada enrolling 11% of subjects. A small number of patients had a variety of eligibility violations (3 subjects) or conduct deviations (29 subjects). These were largely not of a serious nature. These deviations do not lead to any limitations in accepting or interpreting the study results.

After conclusion of the study, one site informed Serono of a systematic deviation from protocol procedures due to misconduct by the site's study coordinator. No indication of treatment group-related bias was apparent, but certain kinds of data from this site could not be independently substantiated from verifiable medical records. This site enrolled 11 patients, and study results were

not different whether or not these 11 patients were included in the analysis. Serono reported no other sites with significant conduct deviations. FDA's audit of 3 sites verified the data reported from these sites and revealed no significant deficiencies in conduct. Therefore, the study conduct was regarded as adequate and the study results accurate as reported.

The subjective aspect of exacerbations and the open label nature of the study lead to use of the between-visit telephone contacts as part of the study design, as described above. These were completed approximately 84% of the time in each treatment group (i.e., an average of 1 missed phone call per subject).

Over the first 6 month period, 95% of Rebif-assigned subjects, and 96% of Avonex-assigned subjects completed treatment. A few of the early treatment-termination subjects continued in the study for evaluations, so that missing data due to subject dropout was less than 3% of subjects. During the course of the 6 months there were intended to be 24 Avonex injections or 72 Rebif injections, depending on assignment. Compliance with at least 90% of planned injections was achieved by 95% of Rebif subjects and 96% of Avonex subjects.

Results of Study XXXXXXXXXX

Baseline

The study was balanced between groups for demographic and baseline characteristics. Most subjects were between the ages of 30 to 49, and 75% were women. The baseline EDSS was predominantly between 1 to 3.5, but ranged from 0 to 5.5 in both groups. Slightly more than half the subjects in each group had exactly 2 exacerbations within the year prior to enrollment, with only a small fraction having 4 or more. The median number of CU active lesions at baseline was 1 in both groups. The mean number of CU lesions at baseline was 2.4 in the Rebif group and 2.9 in the Avonex group. However, this difference in mean values was substantially related to a single subject in the Avonex group with 83 CU lesions at baseline. With exclusion of this subject, the Avonex group mean was 2.6, not substantially different from the Rebif group. Of note, CU lesion count is not a normally-distributed measure within this population; therefore, the median provides a more informative measure of central tendency. The median CU lesion count was the same in the two groups (1.0). Thus, there was not an important imbalance observed between groups on any baseline evaluation.

Results at 6 Months

At the end of the 6 month period 74.9% of the Rebif subjects and 63.3% of the Avonex subjects were exacerbation-free. Thus, the relative risk of *not* having an exacerbation was 1.18 (i.e., Rebif-treated patients were 1.18 times more likely to be relapse-free). This outcome was statistically significant between the groups ($p<0.001$) when tested according to the prospectively-planned logistic regression method. Most subjects who experienced an exacerbation had only one during the 6-month period; there were 98 exacerbations occurring in 85 Rebif-treated subjects and 132 exacerbations occurring in 124 Avonex-treated subjects. Sensitivity analyses for the small amounts of missing data do not indicate any important differences from the primary result.

The percentages of subjects *with* an exacerbation (a more commonly used parameter) were 25.1% in the Rebif group and 36.7% in the Avonex group. The relative risk of having at least one exacerbation was 0.68 (i.e., Rebif-treated patients were 0.68 times as likely to experience an exacerbation). Another frequently used parameter in many MS studies is the exacerbation rate. Patients who had more than one exacerbation would be considered as being more affected (less favorable) than those who had experienced just one exacerbation. In this study, the exacerbation rate (per patient) per 6 months was 0.39 in the Avonex group versus 0.29 in the Rebif group, with a relative rate of Rebif/Avonex of 0.74.

Most exacerbations were ascertained at planned subject visits to the study site. However, roughly 40% of confirmed exacerbations (41% Rebif, 36% Avonex) were ascertained on the basis of unscheduled examinations prompted by either spontaneous patient calls or planned visit-intermediate phone calls. The between-group difference in exacerbation incidence was observed both in those exacerbations ascertained at the scheduled evaluating physician exams, and in those ascertained from symptom-prompted unscheduled exams. The treatment effect on exacerbations was generally consistent within subject subsets based on gender, age, geographic region, and time-frame of enrollment into the study. There were also consistent effects on subsets based on baseline MRI findings. As noted above, there were unequal mean values for the baseline CU lesion count, although in totality, the groups were adequately balanced at baseline with regard to this parameter. The baseline MRI lesion activity modestly predicts the propensity to have a future exacerbation. Nonetheless, the fraction of exacerbation-free patients in the Rebif-treated group exceeded that in the Avonex-treated group in both the higher and lower baseline lesion count subsets, whether categorized on the basis of baseline CU lesion count, T1-active lesion count, or T2-active lesion count. The distribution of exacerbations by severity (mild, moderate, severe) was similar in both groups (28 and 30% mild; 40 and 37% moderate; 24 and 23% severe, for Rebif and Avonex, respectively, with approximately 10% not adequately recorded), but with reduced incidence of exacerbations in the Rebif group compared to the Avonex group for all three severities. In summary, the primary endpoint of the proportion of patients who were exacerbation-free was greater in the Rebif group compared to the Avonex group. This finding was robust to various explorations of the data, and was not due to any known imbalances at baseline between the groups.

The main secondary endpoint was the effect on CU active lesions on MRI. A small number of study sites were prospectively identified as unable to perform the MRI scans, so that there were 650 subjects (325 patients per treatment group) included in the MRI assessments. After the planned 6 monthly MRI scan sets were analyzed, the mean number of CU active lesions per scan was 0.7 in the Rebif group and 1.3 in the Avonex group. This was statiscally significantl($p<0.001$) according to the prospectively-planned nonparametric ANCOVA method, which included the baseline number of CU lesions as a covariate. Unlike the baseline analysis (which was based on a single set of scans, rather than the average across 6), there were no extreme outliers in the 6 month results (range 0 to 16.3 Rebif; 0 to 19.8 Avonex). The difference between groups in the number of CU active lesions became progressively larger during the course of the 6-month period.

Safety analyses did not reveal any adverse reactions of a nature not previously recognized to be a potential risk associated with the use of interferon beta. There were, however, differences in the frequency of certain adverse reactions between the two groups. Injection site reactions were much more frequent in the Rebif group than the Avonex group. This difference was not unexpected,

given that Rebif is administered subcutaneously, whereas Avonex is administered intramuscularly. Skin reactions are much more readily observable than reactions within muscle. Hepatic enzyme increases and leukopenia or lymphopenia were also observed more frequently in the Rebif group. As discussed in Dr. Rask's review, these differences were not of a significant nature.

Study results at 1 year

Serono continued Study XXXXXXXXXX in a controlled manner through 48 weeks. Quality Assurance (QA) procedures were applied to study data from the first 24 weeks while the succeeding portion of the study was ongoing. After QA procedures were completed, the 24-week database was locked and study analyses were conducted, unblinding that portion of the study. The 24 week results were made known to the investigators prior to completion of the entire study. However, most patients had completed or were nearing completion of the 48 week study participation by the time the 24 week results were revealed. Thus, there is, at most, very limited potential impact upon the study results from the slightly early unblinding of study results. Serono has supplied analyses of the 48-week results to the BLA along with datasets supporting these analyses. However, the complete, final study report for the period through week 48 has not been completed by Serono as of yet. The results supplied to CBER have received preliminary review. At this time, they provide supportive data, particularly concerning specific limited issues. The primary evidence for the comparison between the two products is the data through Week 24. The 48-week results of this study are illustrated in the summary tables included in the Appendix of this document.

Through the 48-week timepoint, 62% and 52% of Rebif- and Avonex-treated subjects were exacerbation free, respectively (table A1). This difference was statistically significant ($p=0.006$) when tested according the prospective analytic method of logistic regression. For the subset of patients who were exacerbation-free at 24 weeks, the proportions that remained exacerbation-free through 48 weeks were essentially the same in both treatment groups (82-83%). Thus, the treatment effect observed during the initial 24 weeks on study was maintained during the succeeding 6 months. For the second 24-week period, the similarity of exacerbation events between the two groups is further supported by the distribution of exacerbation severities, which was again essentially the same across the two groups (Table A4).

During the second 6 months of the study, subject retention was adequate. Fewer patients discontinued treatment than had during the first 6 months (8 Rebif, 9 Avonex). Patient contacts were less frequent, and as expected, the fraction of exacerbations ascertained at the scheduled neurological exams (every 3 months) was slightly higher than during the prior 24 weeks (Table A2). However, the number of neurological exams on unscheduled visits were similar between the two groups, as was the fraction of these unscheduled exams that lead to confirmation of an exacerbation. There were somewhat larger numbers of unscheduled patient visits not prompting a neurological exam, such as for AE evaluation or clinical laboratory repeat evaluation. This is consistent with expectations from the first 24 weeks, where modestly higher AE rates and laboratory abnormalities were seen.

Only a T2 MRI was conducted at the 48-week timepoint. To enhance the interpretation of the 48 week results, the Week 24 T2 MRI and the Week 48 T2 MRI were assessed for T2 active lesions, using identical intervals for each (i.e., active lesions at week 24 compared to baseline and active

lesions at week 48 compared to week 24). The result is shown in table A5, which shows a mean number of T2 active lesions lower in the Rebif group than in the Avonex group at both the Week 24 and Week 48 evaluation. The apparently larger mean difference between groups over the first 24 weeks than over the next 24 weeks was dependent in part upon a single Avonex subject with an unusually large number of active lesions (43) seen on the Week 24 examination. MRI scan data from MS trials are generally not normally distributed, and parameters such as mean must be interpreted with attention to the effect of outliers. The percentage of subjects with their scan showing at least 1 active lesion was also lower in the Rebif group than in the Avonex group. This analysis is insensitive to any outlier effect from a few scans with a large numbers of lesions. Of note, the between-group difference observed in comparing T2 active lesions at week 24 and week 0 is slightly larger than that seen by the 6 sequential scan average of CU lesions through week 24 noted above (1.3 CU lesions Avonex, 0.7 Rebif).

As discussed, more new or enlarging lesions were observed in the first 24 weeks in Avonex-treated patients than in Rebif-treated patients. During the second 24 weeks, the development of similar numbers of lesions in the 2 groups would have been consistent with maintenance of the treatment effect. Instead, these data show additional differences favoring Rebif in new or enlarging lesions during the second 24 weeks. As with exacerbations, there is no suggestion of any reversal in the treatment effect.

Study Results on Antibody Formation

Samples for evaluation of antibody formation were obtained at baseline, Week 24 and Week 48. Serono completed the Week 48 samples only, and supplied these analyses. The antibody assay procedure consisted of an initial ELISA screen on all samples. Only the samples showing binding antibodies by ELISA were assessed with the neutralizing assay. Antibody formation rates were higher in the Rebif group, as shown in table A3. Importantly, however, the rates of antibody formation to these molecules are not directly comparable, because the assays performed by Serono measured antibodies by their ability to bind Rebif. It is possible that some patients who received Avonex developed antibodies to Avonex but not Rebif. Such antibodies would not be identified in the assays used by Serono. Thus, there was the potential to differentially underestimate the rate of antibody formation in the Avonex group.

In the Rebif group, there was no association between antibody status and the probability of remaining exacerbation-free, for either the Week 0–24 or the Week 24–48 period (Table A6). Comparisons between the 2 treatment groups with respect to antibody status and clinical outcome demonstrated that all subsets of Rebif-treated patients, categorized by antibody titer, experienced lower exacerbation rates than Avonex-treated patients.

MRI outcome was also examined by antibody status. Rebif patients with antibodies had higher mean CU lesion counts over the first 24 weeks than did Rebif patients without antibodies; however, the median values suggest this difference may be related to several patients with unusually large CU lesion counts (Table A7). Of note, the mean and median CU lesion counts in the Rebif group subset with higher titers were lower than CU lesion counts in the Avonex group as a whole, and in the subset who were antibody-negative.

Examination of the single T2 scan results at Week 24 (compared to baseline) and Week 48 (compared to the Week 24 T2 scan) yielded similar findings (Table A8). This is a useful observation, as it might be hypothesized that an antibody-related effect on MRI lesion outcome would be more likely apparent in the second half of this study, given that it takes time for antibodies to develop in response to treatment. Thus, data through 48 weeks suggest that antibody formation does not affect either clinical or MRI outcomes.

Regardless of any potential effects that might be hypothesized for antibodies, patients on Rebif were more likely to remain free of clinical exacerbations at 24 and 48 weeks; and, importantly, patients on Rebif who developed antibodies (as well as those who did not) were more likely to remain exacerbation-free than patients on Avonex.

Assessment of Study XXXXXXXXXX Design and Results

It is important to view the design and results of Study XXXXXXXXXX in proper context. Several large, multicenter trials of interferon betas have been conducted in MS over the past 10 years, and the effects of beta interferons in MS have been well-characterized. These studies have provided both FDA and the medical community with considerable experience in evaluating the design and results of clinical studies. Betaseron and Avonex, the two interferon betas presently approved for treatment of MS, were shown to decrease the frequency of clinical exacerbations, compared to placebo, by approximately one-third. Study XXXXXXXXXX was the first clinical trial to directly compare the effects of interferon betas, Rebif and Avonex, in a large multicenter clinical study, and it is useful to consider the study design and results within the framework of the prior placebo-controlled experience.

Selection of Primary Endpoint

Serono selected the occurrence of clinical exacerbations as the primary efficacy outcome. The Avonex approved labeling indicates benefit on both disability and exacerbations, and Serono's proposed Rebif labeling indicates the same claimed benefits. Thus, a focus solely upon exacerbations does not address the outcome of disability. However, exacerbations are important events to patients, and the agency has an established regulatory history acknowledging an effect on exacerbations alone as a clinically meaningful benefit. Betaseron was approved in 1993 based solely on showing a reduction in exacerbations. Several years later CDER approved glatiramer acetate (Copaxone) based only on exacerbation reduction. Additionally, as noted above, the labeled indicated benefits of Avonex include reduction in exacerbations. These products have all gained support in the medical community. Patients in earlier stages of MS can experience substantial remission in impairment over time. However, complete remission can require weeks to months, and in many cases remission is not complete. Thus, exacerbations are a relevant aspect of the disease for study, and reduction in exacerbations is a meaningful benefit.

This study was not designed to assess the broad range of actions of Rebif. It was designed to address the requirements of orphan drug regulations to gain early marketing approval. The regulations state that "Clinically superior means that a drug is shown to provide a significant therapeutic advantage" and may be accomplished in one of three ways, including "… as assessed by an effect on a clinically meaningful endpoint …". Orphan drug regulations do not state that all

known clinical actions of a product must be shown superior to the competitor. Rather, superior effectiveness as shown on a single meaningful clinical endpoint is sufficient. Serono's selected study endpoint is clinically meaningful, and appears to be fully in keeping with the intent and requirements of the orphan drug regulations.

Open Label Study Design and Ascertainment of Exacerbations

Exacerbation assessments are somewhat subjective. Exacerbations are best assessed within 1 to 2 days from onset. In the context of a clinical study, this requires that subjects bring symptoms that are potential exacerbations to the attention of the study investigators. Study investigators must then examine subjects to determine whether clinical symptoms and signs more likely represent a temporary worsening of the subject's existing neurologic impairment, or whether the change represents a new impairment that should be classified as an exacerbation. There is a subjective component to this assessment, particularly when the exacerbation is of mild severity. For the reasons cited previously (see "Objective and Design of Serono Study XXXXXXXXXX"), this study was open-label. Knowledge of treatment assignment had the potential to bias the results. Serono addressed this issue in two ways:

1) The study employed frequent contacts between study subjects and site personnel to reduce the potential for study subjects to influence the ascertainment of new exacerbations by the investigators. There were monthly visits and phone contacts midway between visits. Study personnel would actively inquire as to any change in clinical status and have the subject seen by the evaluating physician if there was potential for an exacerbation to be in progress. Thus, even if the subject minimized the import of their symptoms to themselves and did not notify the study site, the subject would be seen by the investigator to ascertain whether the symptoms met the protocol definition of an exacerbation. Mild exacerbations that appeared and fully resolved within the two week period between contacts remain a possible gap in ascertainment. However, such exacerbations constitute a small fraction of all exacerbations, and of the least importance. Of note, differences between treatment groups in the incidences of mild, moderate as well as severe exacerbations were observed.

2) To reduce the potential for study investigator bias in confirming or rejecting a potential exacerbation, there were separate treating and evaluating investigators, with the evaluating investigator blinded to treatment assignment. In order to maintain the blind during contact with evaluating investigators, subjects kept their injection sites fully covered and did not discuss AEs. Thus, bias due to knowledge of the treatment assignment should not have entered into the process of confirming exacerbations.

The degree of subject bias in Study XXXXXXXXXX is unknown. Both groups were treated with active agents believed to be effective (as opposed to treatment with a known inactive substance as in placebo-controlled studies), and patient preference may not necessarily have favored Rebif, given the difference in the frequency of injections. Subjects in both treatment groups were substantially compliant with injection regimens, indicating a willingness to comply with study procedures in both groups.

Prior experience with MS studies is relevant. Studies of interferon betas and other products for MS have included exacerbation occurrence as either a primary or secondary endpoint. All the interferon

betas, irrespective of injection frequency or route, cause local injection site and systemic flu-like symptoms that likely lead to patient unblinding. This is well-recognized in the neurologic community. In order to address the potential for bias related to investigator unblinding due to adverse effects, these studies have commonly employed blinded, separate evaluating physicians. Procedures such as limiting subject discussion of AEs with the evaluating physician and having the subjects fully covered to hide injection sites have also been employed to protect the evaluating physician's blinding. As noted above, several of these studies have contributed to the central demonstration of effectiveness in reducing exacerbations and have led to labeling claims. Serono's Study XXXXXXXXXX employed these accepted techniques to reduce the potential for bias, and included subject contact every two weeks to ensure robust ascertainment of exacerbations. Most other studies used less frequent scheduled site contacts and greater reliance on spontaneous call-in by subjects to report potential exacerbations. Therefore, while exacerbation ascertainment and assessment contain subjective elements potentially biased by unblinding, Study XXXXXXXXXX employed standard, accepted techniques to minimize these sources of bias, and scheduling that was more rigorous than used in prior studies to maximize ascertainment.

Duration of Study

Multiple sclerosis is a chronic disease, and warrants long-term treatment. Phase 3 studies of beta interferons in MS, including prior studies of Rebif and Avonex, have generally been of 2 years duration or longer. Although the primary endpoint assessment in this study occurred after 6 months, prior experience has shown that early salutary effects of interferons on exacerbations persist. Consistent with prior experience, there was no suggestion that the early efficacy of Rebif diminished over time in the 2-year placebo-controlled trial. Similarly, preliminary analysis of the 48-week data in Study XXXXXXXXXX indicates persistence of effect. Therefore, a 6-month primary study period constitutes an adequate examination of the relative efficacy of two beta interferons, when each has previously demonstrated persistent efficacy throughout a two year study period.

Effect on Exacerbations

The observed difference in the incidence of exacerbations in this study was robust to exploration of the data. No geographic region or single site drove the results, and no anomalous subsets were identified. The treatment effect was apparent on severe, as well as mild exacerbations, and was observed in subject subsets both with and without active MRI lesions at baseline. Table 1 summarizes the experience with interferon betas in major randomized controlled studies. None of the interferon betas completely eliminate exacerbations. The relative reduction in incidence of exacerbations (or relative exacerbation rates) seen in Study XXXXXXXXXX is slightly less than that observed in studies of Betaseron or Rebif compared to placebo, somewhat larger than seen with Avonex vs. placebo in the initial phase 3 study, and comparable to the effect size observed in the Avonex study of Early MS. Moreover, the relative reduction in exacerbation rates observed with Rebif in Study XXXXXXXXXX was larger than that typically observed in investigations designed to assess various dose levels of a single interferon beta.

MRI Endpoints

MRI studies can be analyzed in a fully blinded manner; therefore, MRI outcomes are less subject to bias. MRI results have consistently provided objective evidence of the activity of interferon betas on brain lesions in MS. In Study XXXXXXXXXX, the demonstration of differences between groups on MRI endpoints was robust to multiple exploratory analyses. It is also important to note that the differential effect of the two products on MRI lesions persisted through the second 24-week study period.

A summary of results of major studies with interferon betas is shown in Tables 1 and 2. All of the MRI techniques are regarded as useful and supportive, and the technique employed by Serono was fully adequate for the intended purpose.

Tbl 1: Major Randomized Controlled Studies of Interferon Beta in Multiple Sclerosis -- Exacerbation and MRI Lesion Rates										
Specific Drug Study ID	Doses Studied	Result Source	Exacerbations Pbo	IFN1	IFN2	Notes	MRI Active Lesion Rate Pbo	IFN1	IFN2	Notes
RRMS or Early MS										
Betaseron Orig. Ph 3 Study	Pbo, 1.6MIU, 8MIU qod	1 & 2	1.31	1.14	0.9	Ann Exac. Rate over 2 yrs	4.9	1.8	2	Active lesions per yr in small subset
AVONEX Orig. Ph 3 Study	Pbo, 30ug qw	1 & 2	0.82	0.67		Over 2 yrs Ann rate	4.8	3.2		Only 2 yr subjects
AVONEX CHAMPS	Pbo, 30ug qw	2	50%	35%		Proportion with at least 1 exacerbation	2.8	1.5		No. of active lesions in first 6 months
Rebif GF6719	Pbo, 22ug, 44ug tiw	2	2.56	1.82	1.73	Rate of relapses over 2 years	0.88	0.17	0.11	CU lesions freq. MRI subset
Rebif GF7480 (Early MS)	Pbo, 22ug qw	2	0.43	0.33		Ann relapse rate over 2 yrs	3	2		median # T2 active lesions
Rebif OWIMS	Pbo, 22, 44 ug qw	2	1.08	1.08	0.87	relapse rate over 1 year	1.7	1.3	0.8	6mo MRI CU lesion
SPMS										
Betaseron N.American Study	Pbo, 5MIU/m2; 8MIU qod	3	0.28	0.2	0.16	ann relapse rate across 3 years	17	4	6	Annual rate of new enhancing lesions during 3 yrs
Betaseron European Study	Pbo, 8MIU qod	2	0.57	0.42		Ann relapse rate across 3 yrs	8.82	3.77		# new or enlarging lesions during first 6 mo, freq MRI subject subset
Rebif SPECTRIMS	Pbo, 22, 44 ug tiw	2	0.71	0.5	0.5	Ann relapse rate	1	0.22	0.11	CU lesions in freq MRI subset

Results Source Notes: 1 – According to approved label; 2 – According to study publication;
3 – Results approximate, taken from figures of scientific meeting presentation

Overall Note: MRI results based on differing methods between studies, and differing parameters reported in publications (e.g., mean vs median)

Tbl 2: Major Randomized Controlled Studies of IFN-beta in MS -- Relative Rates Treatment Effect								
Specific Drug Study ID	Doses Studied	Result Source	Relative Rates of Exacerbation			Relative rates of MRI Lesions		
			IFN1/Pbo	IFN2/Pbo	IFN2/IFN1	IFN1/Pbo	IFN2/Pbo	IFN2/IFN1
RRMS or Early MS								
Betaseron Orig. Ph 3 Study	Pbo, 1.6MIU, 8MIU qod	1 & 2	0.87	0.69	0.79	0.37	0.41	1.11
AVONEX Orig. Ph 3 Study	Pbo, 30ug qw	1 & 2	0.82			0.67		
AVONEX CHAMPS (Early MS)	Pbo, 30ug qw	2	0.70			0.54		
Rebif GF6719	Pbo, 22ug, 44ug tiw	2	0.71	0.68	0.95	0.19	0.13	0.65
Rebif GF7480 (Early MS)	Pbo, 22ug qw	2	0.77			0.67		
Rebif OWIMS	Pbo, 22, 44 ug qw	2	1.00	0.81	0.81	0.76	0.47	0.62
SPMS								
Betaseron N.American Study	Pbo, 5MIU/m2; 8MIU qod	3	0.71	0.57	0.80	0.24	0.35	1.50
Betaseron European Study	Pbo, 8MIU qod	2	0.74			0.43		
Rebif SPECTRIMS	Pbo, 22, 44 ug tiw	2	0.70	0.70	1.00	0.22	0.11	0.50

Results Source Notes: 1 – According to approved label; 2 – According to study publication;
3 – Results approximate, taken from figures of scientific meeting presentation

Overall Note: MRI results based on differing methods between studies, and differing parameters reported in publications (e.g., mean vs median). Relative rates calculated from available parameters.

Concordance of MRI Endpoints and Clinical Exacerbations

For the specific product class of interferon betas, multiple studies have shown a general concordance of effects on exacerbations and MRI lesions. The relative reduction in rates of MRI active lesions has generally been more than the relative reduction in exacerbation rates (Table 2). MRI concordance in the direction of relative effects can provide supportive evidence regarding the treatment effect, but MRI results alone do not constitute evidence of clinical efficacy. MRI results cannot be given equal weight to the clinical evidence, nor can the results be used to estimate the actual clinical effect size.

Assessment of Study XXXXXXXXXX as Evidence of Effectiveness

The FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998, addresses the quality and quantity of evidence to support a proposed claim. While the Agency sometimes seeks two independent studies to support a demonstration of effectiveness, the document also recognizes that a single phase 3 clinical study of an appropriate design with persuasive results, when accompanied by supportive evidence, can be sufficient, as has been the case for interferon betas in MS.

Study XXXXXXXXXX was a multicenter trial, with good uniformity of results across centers and across a number of different subject subsets. The findings were statistically robust, internally consistent, and substantiated on sensitivity analyses. Treatment effects were apparent both on exacerbations overall, as well as on exacerbations subdivided by severity. The MRI results were supportive and also statistically robust.

Interferon betas have been investigated in MS for over a decade and there is substantial experience in the design of adequate studies with these products. Betaseron and Avonex were each approved based upon a single phase 3 study that incorporated many of the attributes that the guidance describes as conveying strength to the evidence. The Betaseron study, much as Study XXXXXXXXXX, showed benefits on the same endpoints: exacerbation rates and MRI lesions. Assessment of the adequacy of Study XXXXXXXXXX may be influenced by the fact that the investigation compared two previously well-studied interferon betas in MS.

The placebo-controlled study of Rebif provides additional evidence of effectiveness, including the finding that efficacy of Rebif persists unabated beyond the 6- to 12-month period.

Assessment of Specific Orphan Drug Issues

The objective of this study was to provide evidence to reach a finding that Avonex and Rebif should not be regarded as the same drug for purposes of orphan drug regulations. This would permit marketing approval to be granted to Serono for Rebif at the present time, rather than waiting until May 2003 when Avonex's exclusivity period expires. To this end, review of the issues required to reach this conclusion is warranted.

Same Drug Issues

Interferon betas are proteins and macromolecules (large molecules). Under orphan drug regulations, a macromolecular drug that contains the same principal molecular structural features but not necessarily all the structural features of another drug could be considered the same drug if not shown to be clinically superior. For proteins, it is noted that minor differences in amino acid sequence and other potentially important differences do not per se exclude a drug from being considered the same if not shown to be clinically superior. These provisions reflect an important reality about proteins–some very small modifications in these large molecules have no effect on the activities, whereas other minor modifications have large effects, potentially resulting in substantial benefits to patients. Similarly, differences in how the active moiety is formulated or administered could make no clinical difference or a very large one. Therefore, under the regulations, such differences do not automatically make the drug a different drug for orphan purposes, but the drug is considered different if shown to be clinically superior (See 21CFR Part 316).

Some have questioned whether a different dose of the identical active agent, if shown superior, should be considered not to be the same drug. That question is not relevant here, because for non-orphan comparability purposes, Avonex and Rebif are not the same drug. Analytic methodology does not provide us with a method to determine that two protein drugs such as Rebif and Avonex from two separate manufacturers are, in fact, identical. The demonstrated clinical superiority of Rebif over Avonex might result from chemical differences in the active molecule, physical differences such as microaggregation, differences in impurities, differences in formulation, differences in route, differences in the injection schedule, differences in the amount of protein given, or any combination of the above. There is no way to determine which of these factors contribute to the observed clinical differences, and under the orphan drug regulatory scheme, there is no need to do so. Recognizing these issues, the orphan drug regulations state that real or potential small physicochemical differences between proteins and macromolecules do not make them different drugs for orphan purposes but, even absent detectable differences, a demonstration of clinical superiority does. Appropriately, Rebif was compared to the formulation, route, dose, and schedule of Avonex currently approved as effective and indicated in the approved labeling of Avonex, and Rebif was found to be superior.

Significant Therapeutic Advantage

Endpoint Selected for the Study

Serono studied a specific clinical efficacy outcome in Study XXXXXXXXXX. A comprehensive study of all previously known efficacy benefits (or of potential, but as yet unproven benefits) was not performed. Again, this is in keeping with the requirements of the orphan drug regulations. The regulations explicitly state that greater effectiveness is "as assessed by effect on a clinically meaningful endpoint." The regulations do not state "all" endpoints, only "a" endpoint. Thus, selection of one appropriate endpoint is sufficient.

As discussed above, exacerbations are a clinically meaningful and important endpoint. An MS exacerbation can substantially lower quality of life for weeks or months. Exacerbations vary greatly in nature and intensity of impairment and can involve partial or complete paralysis, difficulty

walking or inability to walk, significant loss of vision, or loss of bowel and bladder control. The general acceptance of the clinical importance of reducing exacerbations was evidenced by the fact that, based on a study in which the only clinical benefit shown was reduction of exacerbations and no effect was demonstrated on lasting disability, an FDA expert advisory committee recommended approval of Betaseron, FDA licensed Betaseron, and many physicians and patients began to use it.

Study XXXXXXXXXX demonstrated an advantage on exacerbations. This advantage was demonstrated on a 24-week endpoint, observed to be maintained on the 48-week outcomes, and can be reasonably expected to persist beyond that time frame, given the prior experience with interferon betas in many large studies.

Effects of Neutralizing Antibodies

A concern regarding this extrapolation is the notable difference in antibody formation rates suggested by the data obtained. However, as described in detail above, the 1-year results are reassuring in this regard. In evaluating whether antibodies might later cause a disappearance of Rebif advantages observed over the first 6 months, the data at one year are quite relevant. The Rebif subjects with the highest antibody titers continued to have fewer exacerbations in the second 6 months than did the Avonex group as a whole, or the Avonex antibody-negative subgroup. Additionally, neither the exacerbation data nor the MRI outcomes at one year suggest that the advantages of Rebif observed at 6 months were reversing.

Some published studies have suggested that the development of anti-interferon antibodies has a negative impact on clinical outcome. However, as discussed above, these trials can not actually distinguish between the possibility that antibody development causes a less favorable clinical course, versus the possibility that subjects who develop interferon antibodies intrinsically have a more active immune systems, leading to a less favorable clinical course. The published analyses are also obfuscated by the fact that many patients who develop antibodies at one point in time will later fail to have antibodies detected, and may remain persistently interferon antibody-negative.

Additionally, there are conflicting study outcomes regarding the impact of antibody formation on efficacy of interferons. In some study subset analyses, no impact was observed. In recognition of this uncertainty, a recent "Report of the Therapeutics and Technology Assessment Subcommittee" of the Academy of Neurology and the MS Council for Clinical Practice Guidelines concluded that the biological effect of neutralizing antibodies is uncertain, although it is possible that antibodies will have some effect on reducing effectiveness. They do not recommend clinical monitoring of patients for antibodies, or make any recommendation regarding treatment of patients who develop antibodies. Consequently, while antibodies are of some concern to the field, there is not adequate evidence to conclude that antibodies lead to a major loss of efficacy, or that the impact of antibodies, if any, will be long lasting.

Magnitude of Treatment Effect Differences

Given that the difference between the two therapies is on a clinically significant and meaningful endpoint, one might also ask whether the proportion of patients benefited (or other measures of the magnitude of benefit on the endpoint) is sufficient to qualify as significant. In Study

XXXXXXXXXX, patients on Rebif had a 32% lower risk of having an exacerbation than patients on Avonex, with 37% of patients on Avonex and 25% of patients on Rebif experiencing relapses in 6 months. While there is no minimum effect size predetermined for trials in MS, the magnitude of this effect is substantial. Comparisons of effects across different trials should be made with great caution because they involve effects observed in different studies, with different sets of patients, over different periods of time, and observed and measured differently over different intervals. Furthermore, comparisons of the same endpoint, i.e., percent of patients without an exacerbation, can be made in various ways, such as absolute difference between groups, ratio of proportions having an exacerbation, and ratio of proportions remaining exacerbation-free. That said, we would note that, viewed in terms of a commonly used and appropriate measure, the relative reduction in exacerbations, the size of the difference in effect between Rebif and Avonex in this trial is on the same order as the size of differences observed in earlier trials between Avonex and placebo and between Betaseron and placebo. Clearly, FDA precedent has recognized that a reduction in exacerbations of the approximate size seen in this study is meaningful by providing labeling for Avonex and Betaseron with a stated claim of benefit on exacerbations. In this matter, this reduction in exacerbations also represents a significant therapeutic benefit to MS patients.

It could be argued that the absolute difference between proportions of patients with exacerbations at 6 months on Rebif and Avonex (37% minus 25%, or 12%) is smaller than differences observed in some placebo-controlled studies. Absolute differences in rates are likely to be particularly sensitive to study differences, including severity of illness in the patient population and study duration, and therefore, especially problematic for cross-study comparisons. Also, absolute differences are likely to be smaller when comparing a superior drug to an already effective drug than when comparing a drug to placebo. For example, suppose the first drug prevents an important morbidity in 90% of patients. Even if the new drug were completely (100%) effective, the absolute difference compared with the first drug would be only 10%, small compared with the absolute effect of the first drug, but likely a very important advance. Finally, and most importantly, independent of findings of any other study, 12% of patients is a substantial portion of patients to benefit. Consequently, a significant therapeutic advantage has been shown by Serono for Rebif over Avonex.

Safety

A final consideration is safety. A biological product such as Rebif must be both safe and effective to warrant approval. Apart from any orphan drug considerations, Rebif has been adequately demonstrated to be safe in the placebo controlled study (see Dr. J. Kaiser's review) in order to be licensable under the Public Health Service Act (PHS Act).

Based on FDA's knowledge of interferon betas in general, and Rebif and Avonex in particular, FDA anticipated differences in the incidence of injection site reactions in the comparative trial. The injection site skin necrosis associated with use of Rebif was not observed with Avonex. However, Rebif-induced skin necrosis is less frequent than observed with Betaseron, and does not seem to pose a serious limitation to the use of the product. No patients required skin grafting or debridement (as seen with Betaseron), and most are able to continue use of the product (see, for example, the narrative in the publication by Radziwill and Courvoisier JNNP, 1999; 67:115).

Unanticipated differences were observed in the incidences of hepatic enzyme elevations and hematologic abnormalities; however, none of these AEs were of sufficient magnitude to alter FDA's previous determination that Rebif is licensable under the PHS Act. Neither hepatic enzyme elevations nor hematologic abnormalities have posed significant problems in clinical studies (see Dr. C. Rask's review). Finally, neither Biogen nor Serono have submitted any data to CBER regarding brain atrophy that would render Rebif unlicensable under the PHS Act.

As discussed above, the orphan drug regulations do not require that safety be superior or even identical between two drugs when a clinical efficacy comparison is employed for the demonstration of being not the "same drug." Therefore, safety considerations do not limit the ability of FDA to make a determination in the present case. The discussion of AEs in the preceding paragraph is not directly relevant to the clinical superiority comparison between Rebif and Avonex. Rather, it is relevant to whether Rebif is licensable. FDA determined in 1998 that Rebif is licensable under the PHS act.

Recommendation

Serono has provided evidence that Rebif is clinically superior to Avonex in reducing exacerbations in MS. Consequently, this review recommends that FDA find Rebif to be not the "same drug" as Avonex, and recommends that Rebif be granted marketing approval at this time.

Appendix: Summary Tables of Results through Week 48

Tbl A1: Exacerbation Status Through Week 48						
	To Week 24		To Week 48		From Wk 24 to Wk 48	
	Avonex n=338	Rebif n=339	Avonex n=338	Rebif n=339	Avonex n=214	Rebif n = 254
No Exacerbation	214 (63%)	254 (75%)	177 (52%)	209 (62%)	177 (83%)	209 (82%)
1 or more Exac.	124 (37%)	85 (25%)	161 (48%)	130 (38%)	37 (17%)	45 (18%)
Relative Rate of at least 1 exac. (Rebif / Avonex)	0.68		0.81		1.02	

Tbl A2: Numbers of Unscheduled Visits and Exacerbation Outcome				
	Avonex n=338		Rebif n=339	
Unscheduled visits	105		142	
No Neuro exam	40		85	
U.Visit with Neuro exam	65	62%	57	40%
U. Visit with Exacerbation Confirmed (%of exams)	44	68%	39	68%
Steroid use at U.Visit with Exac (% of Exac)	16	36%	20	51%
Scheduled Neuro exam with Exac Confirmed	35		42	

Tbl A3: Antibody Development at Week 48		
Ab Status	Avonex	Rebif
ELISA positive	38 / 294 13%	146 / 299 49%
Neutralizing Pos (any titer)	15 / 294 5%	103 / 298 35%
Neutr. Pos titer >= 5	15 / 294 5%	99 / 298 33%
Neutr pos titer >= 20	7 / 294 2%	75 / 298 25%

Tbl A4: Exacerbations by Severity

	To Week 24				To Week 48				From Wk 24 to Wk 48			
	Avonex		Rebif		Avonex		Rebif		Avonex		Rebif	
	n	%	n	%	n	%	n	%	n	%	n	%
Total # Exac.	132		98		212		180		80		82	
Mild	40	30%	27	28%	66	31%	52	29%	26	33%	25	30%
Moderate	49	37%	39	40%	82	39%	78	43%	33	41%	39	48%
Severe	30	23%	23	23%	40	19%	34	19%	10	13%	11	13%
Grade N. Avail	13	10%	9	9%	24	11%	16	9%	11	14%	7	9%

Tbl A5: T2 MRI Results at Week 24 and 48

Study Time	parameter	Number of New Active T2 Lesions (compared with 24 wks earlier)		% of Patients with Active Scan	
		Avonex	Rebif	Avonex	Rebif
Week 24	n	312	315	312	315
	mean	1.7	0.9	51%	31%
	median	1	0		
Week 48	n	303	304	303	304
	mean	1.2	0.9	37%	25%
	median	0	0		

Tbl A6: Exacerbation Free Status By Subsets based on Week 48 Neutralizing Ab Status

Neutr. Ab Status	Weeks 0 to 24						Weeks 0 to 48						Weeks 25 to 48					
	Avonex			Rebif			Avonex			Rebif			Avonex			Rebif		
	# at risk	# Exac Free	%	# at risk	# Exac Free	%	# at risk	# Exac Free	%	# at risk	# Exac Free	%	# at risk	# Exac Free	%	# at risk	# Exac Free	%
Neg	279	171	61%	195	146	75%	279	139	50%	195	123	63%	171	139	81%	146	123	84%
Any Pos	15	13	87%	103	78	76%	15	12	80%	103	62	60%	13	12	92%	78	62	79%
+ titer <20	8	7	88%	28	21	75%	8	6	75%	28	16	57%	7	6	86%	21	16	76%
+ titer >=20	7	6	86%	75	57	76%	7	6	86%	75	46	61%	6	6	100%	57	46	81%
+ titer >=100	1	1	100%	49	40	82%	1	1	100%	49	32	65%	1	1	100%	40	32	80%
+ titer >=500	1	1	100%	21	14	67%	1	1	100%	21	12	57%	1	1	100%	14	12	86%

Tbl A7: CU MRI Lesion Outcome By Neutr. Ab Status - 24 weeks			
Neutralizing Ab Status	parameter	Avonex n = 294	Rebif n = 298
Negative	n	269	185
	mean	1.33	0.48
	median	0.33	0.17
Any Pos	n	15	101
	mean	0.82	1.04
	median	0.4	0
Positive titer < 20	n	8	27
	mean	0.64	0.93
	median	0.37	0
Positive titer >= 20	n	7	74
	mean	1.03	1.08
	median	0.67	0.17

Tbl A8: T2 MRI Active Lesions Single Scan Outcome by Neutr. Ab Status					
Neutralizing Ab Status	parameter	Avonex Wk 24 scan	Avonex Wk 48 scan	Rebif Wk 24 scan	Rebif Wk 48 scan
Negative	n	264	260	182	180
	mean	1.69	1.08	0.66	0.51
	median	1	0	0	0
Any Pos	n	15	15	101	98
	mean	1.2	1.2	1.3	1.33
	median	0	0	0	0
Positive titer < 20	n	8	8	27	26
	mean	1	0.13	0.7	0.19
	median	0	0	0	0
Positive titer >= 20	n	7	7	74	72
	mean	1.43	2.43	1.51	1.74
	median	1	0	0	0